

## BCL6-mediated repression of p53 is critical for leukemia stem cell survival in chronic myeloid leukemia.

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### Public Summary:

Chronic myeloid leukemia (CML) is induced by the oncogenic BCR-ABL1 tyrosine kinase and can be effectively treated for many years with tyrosine kinase inhibitors (TKIs). However, unless CML patients receive life-long TKI treatment, leukemia will eventually recur; this is attributed to the failure of TKI treatment to eradicate leukemia-initiating cells (LICs). Recent work demonstrated that FoxO factors are critical for maintenance of CML-initiating cells; however, the mechanism of FoxO-dependent leukemia initiation remained elusive. Here, we identified the BCL6 protooncogene as a critical effector downstream of FoxO in self-renewal signaling of CML-initiating cells. BCL6 represses Arf and p53 in CML cells and is required for colony formation and initiation of leukemia. Importantly, peptide inhibition of BCL6 in human CML cells compromises colony formation and leukemia initiation in transplant recipients and selectively eradicates CD34(+) CD38(-) LICs in patient-derived CML samples. These findings suggest that pharmacological inhibition of BCL6 may represent a novel strategy to eradicate LICs in CML. Clinical validation of this concept could limit the duration of TKI treatment in CML patients, which is currently life-long, and substantially decrease the risk of blast crisis transformation.

### Scientific Abstract:

Chronic myeloid leukemia (CML) is induced by the oncogenic BCR-ABL1 tyrosine kinase and can be effectively treated for many years with tyrosine kinase inhibitors (TKIs). However, unless CML patients receive life-long TKI treatment, leukemia will eventually recur; this is attributed to the failure of TKI treatment to eradicate leukemia-initiating cells (LICs). Recent work demonstrated that FoxO factors are critical for maintenance of CML-initiating cells; however, the mechanism of FoxO-dependent leukemia initiation remained elusive. Here, we identified the BCL6 protooncogene as a critical effector downstream of FoxO in self-renewal signaling of CML-initiating cells. BCL6 represses Arf and p53 in CML cells and is required for colony formation and initiation of leukemia. Importantly, peptide inhibition of BCL6 in human CML cells compromises colony formation and leukemia initiation in transplant recipients and selectively eradicates CD34(+) CD38(-) LICs in patient-derived CML samples. These findings suggest that pharmacological inhibition of BCL6 may represent a novel strategy to eradicate LICs in CML. Clinical validation of this concept could limit the duration of TKI treatment in CML patients, which is currently life-long, and substantially decrease the risk of blast crisis transformation.

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